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Taste and smell changes in cancer patients

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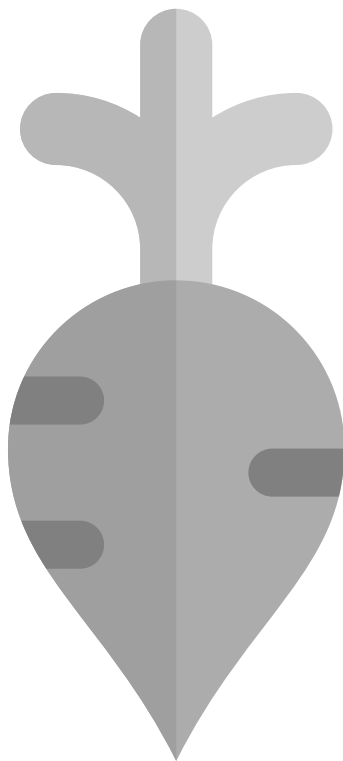
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Metallic taste in cancer patients treated with systemic therapy: a questionnaire-based study

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Abstract

A metallic taste is reported by cancer patients as a side effect of systemic therapy. Despite the high prevalence, this taste alteration has received limited attention. The present study investigated: 1) the prevalence of metallic taste in cancer patients treated with systemic therapy; 2) possible predictors of metallic taste; 3) characteristics of metallic taste. A heterogeneous population of 127 cancer patients, who had received systemic treatment in the past year or were still on treatment, completed a questionnaire developed for this study. Fifty-eight of 127 (46%) patients reported taste changes in the preceding week. Of these patients, 20 (34%) reported a metallic taste. Patients treated with chemotherapy, concomitant radiotherapy, as well as targeted therapy reported metallic taste. Women experienced metallic taste more often than men. Patients experiencing a metallic taste also reported more frequently that they were bothered by sour food and that everything tasted bitter. The experience of metallic taste was highly variable among patients. In conclusion, metallic taste is a frequently experienced taste alteration by cancer patients. Patients treated with chemotherapy, concomitant radiotherapy, and targeted therapy are all at risk for this taste alteration. However, not all patients reported this alteration as bothersome.

Keywords: metallic taste, taste changes, cancer patients, systemic therapy

Introduction

Taste changes are common in cancer patients as a result of systemic therapy. Taste changes have been associated with a decreased appetite, dietary intake, and quality of life [1-7]. The taste perception of cancer patients can be absent (ageusia), decreased (hypogeusia), increased (hypergeusia), distorted (dysgeusia), or taste can be perceived without an external stimulus (phantogeusia) [8].

Most studies regarding taste changes in cancer patients have focused on the presence of taste changes in general (yes/no) or investigated changes in the perception of the primary tastes sweet, sour, salty, and bitter. A metallic taste is a typical taste alteration frequently reported by cancer patients [9]. A recent review showed a prevalence of metallic taste ranging from 10% to 78% in cancer patients treated with chemotherapy [10]. Despite the high prevalence of metallic taste, this taste alteration has received limited attention. A cross-sectional study among patients with various cancer types showed that patients, who reported weight loss since the start of treatment, were more likely to report an increased sensitivity to metallic and salty taste, compared to patients who reported weight gain or no weight change [11]. The consequences of metallic taste regarding food intake, food preference, and quality of life are unknown. To the best of our knowledge, no study has focused on metallic taste specifically, so far.

The present study aimed to investigate the prevalence of metallic taste in cancer patients treated with systemic therapy and to explore possible predictors of metallic taste regarding age, gender, treatment type, time since most recent treatment, and factors related to taste changes. Furthermore, characteristics of metallic taste, including the perceived intensity, the duration, and consequences regarding food intake were explored.

Methods

Study population

Cancer patients who had received systemic treatment in the past year or were still on treatment, with the ability to comprehend Dutch (both reading and writing), were eligible for inclusion. Patients were heterogeneous regarding cancer type and treatment. During a time period of 3 wk, all eligible patients were invited to participate during their regular follow-up visit at the Medical Oncology outpatient clinic of the University Medical Center Groningen. Moreover, eligible hospitalized patients were asked to participate during a period of 1 wk. During the 3-wk time period that patients visited the outpatient clinic, all patients were asked to participate at the discretion of their treating physician. Eligible patients admitted to the ward were identified at the discretion of the attending physician. Patients received the questionnaire from the treating physician or nurse during the outpatient visits or from a researcher during hospitalization. The patients completed the questionnaire during the visit of the outpatient clinic or during hospitalization. The study was conducted in accordance with the Dutch regulations for research.

Questionnaire

A questionnaire was constructed for the present study, since no Dutch questionnaire was available that addressed our specific research questions. Most questions were based on the English version of a validated chemotherapy-induced taste alteration scale (CiTas) [12]. The scale of the Japanese CiTas appeared not to be appropriate for the Dutch population, since no appropriate translation of the English grading (no, slightly, somewhat, quite, and very much) could be established. Therefore, the scale was altered in a 4-point scale as used in the questionnaire of the European Organisation for Research and Treatment of Cancer (EORTC), the EORTC QLQ- C30 (1 = not at all, 2 = a little, 3 = quite a bit, and 4 = very much) [13]. English questions of the CiTas were translated into Dutch and back to English by the researchers and a bilingual physician. Furthermore, questions concerning the ability to detect taste, food aversions, factors that might affect taste (e.g., dry mouth), and metallic taste were added [8,14,15]. Adaptations regarding responding scales were made to make the questionnaire uniform. An initial draft of the questionnaire was reviewed by an experienced panel consisting of five researchers

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in the field of tasting, a medical oncologist, and a data analyst. Next, the draft of the questionnaire was pilot-tested among 30 cancer patients, heterogeneous in age, cancer type, and treatment, to ensure all questions were clear and were interpreted as intended. Based on this pilot, several questions were added or adapted. For example, the questions regarding trouble keeping food down and dry mouth were added, since several patients came up with these symptoms related to their taste changes. Moreover, examples of certain foods that raise an aversion (such as the question “Sweet food bothers me”) were removed from the questionnaire, as several patients based their answers on the examples of foods instead of the taste.

The finalized 47-item questionnaire consisted of three parts (see supplementary material). The first part contained eight questions regarding disease and treatment. The last question of the first part was: “Have you experienced a change in taste since your diagnosis?” When patients ticked the box “yes,” they experienced a change in taste somewhere during their course of the disease. All patients filled out this part. The second part consisted of 30 closed questions regarding taste, smell, appetite, food aversions, and factors associated with taste. This part was only filled out by patients who reported to have taste changes in the preceding week. This time window was used to minimize the relay on memory to assess a recent and precise experienced taste sensation. The last two questions of the second part were: “Have you experienced certain foods to taste differently than before your diagnosis?” and “Have you experienced a continuous taste in your mouth that you did not experience before your diagnosis?” The response options included: blood, bitter, something chemical, something musty, drugs, metallic, sweet, salty, sour, and “other, namely.” Multiple answers were possible. Patients who ticked the box “metallic” for one of these questions or for both questions were defined as experiencing a metallic taste. Only this last category of patients filled out the last part of the questionnaire. This third part contained five statements regarding the intensity, the consequences regarding the ability to eat in general and certain foods, and the evoked sensation (by food products or a continuous sensation) of metallic taste using the same 4-point scale as previously mentioned.

Statistical analysis

Descriptive statistics are presented as mean \pm standard deviation or percentages. Multiple logistic regression (forward stepwise likelihood ratio method) was used to investigate the relation between metallic taste and several parameters listed in the following sections. Two models were used. The first model explored the relation between metallic taste and characteristics of patients and treatment. The model included the following parameters: age, gender, treatment type, and time since most recent treatment (N = 58). The second model additionally included the responses regarding taste changes and factors associated with taste changes. Patients who filled out “I do not know” at one or more questions were excluded from analysis, resulting in 38 patients included in model 2. As this number of patients is low compared to the number of tested parameters, overfitting may occur. Therefore, a third analysis was used with only significant parameters from model 2 to maximize the sample size. The model included only age, gender, treatment type, time since most recent treatment, and the response on “sour food bothers me,” “fatty food bothers me,” and “everything tastes bitter” (N = 54).

To explore the relation between metallic taste and treatment type, treatments were divided into the following treatment groups: platinum-based chemotherapy, taxane-based chemotherapy, other chemotherapy, hormonal therapy, tyrosine kinase inhibitor therapy, other targeted therapy, and concomitant systemic treatment with radiotherapy. The time since most recent treatment was divided into less than 1 mo ago, between 1 and 3 mo ago, and more than 3 mo ago. Patients who received daily treatment were grouped into the category of most recent treatment less than 1 mo ago. Statistical analyses were performed using SPSS, version 22 (SPSS Inc. Chicago, IL). A two-tailed p-value <0.05 was considered statistically significant.

Results

Characteristics of study population

A total of 255 patients were asked to participate in the study. Of these patients, 127 (50%) filled out the questionnaire. The characteristics of the patients are shown in Table 1.

Table 1 Characteristics of the patients.

	Cancer patients (N = 127)
Age (years), mean \pm SD	56.8 \pm 13.7
Gender, male N (%)	54 (43)
Treatment group, N (%)	
Platinum-based CT	27 (21)
Taxane-based CT	9 (7)
Other CT	33 (26)
Hormonal therapy	13 (10)
TKI treatment	13 (10)
Other targeted treatment	23 (18)
Concomitant radiotherapy	9 (7)
Most recent treatment, N (%)	
< 1 month ago	109 (86)
Between 1 - 3 months ago	8 (6)
> 3 months ago	10 (8)
Number of received CT courses, N (%)	
1	9 (13)
2	14 (20)
3	16 (23)
4	16 (23)
5	3 (4)
6	8 (12)
> 6	3 (4)
Duration of treatment (HT and TT), N (%)	
< 1 month	4 (8)
Between 1 - 3 months	17 (35)
> 3 months	28 (57)

CT = chemotherapy, TKI = tyrosine kinase inhibitors, HT = hormonal therapy,

TT = targeted therapy.

Prevalence of taste changes

Of the 127 cancer patients, 79 (62%) reported taste changes since diagnosis. Of these 79 patients, 58 (46% of total) had taste changes in the preceding week.

Of the 127 patients, 20 (16%) patients (5 male, 15 female) reported a metallic taste in their mouth and/or that food had a metallic taste. Thus, 34% of the 58 patients who had taste changes in the preceding week experienced a metallic taste (since only patients who reported to have taste changes in the preceding week filled out the questions regarding metallic taste). Patients treated with chemotherapy, concomitant radiotherapy, as well as targeted therapy reported metallic taste with a prevalence of at least 10% (Table 2). Of all treatments, taxane-based chemotherapy had the highest prevalence of metallic taste (4 out of 9; 44%).

Table 2 Prevalence of taste changes and metallic taste across treatment groups.

Treatment group (TG)	N	Taste changes since diagnosis N (% of TG)	Taste changes preceding week N (% of TG)	Metallic taste N (% of TG)
Platinum-based CT	27	20 (74)	12 (44)	4 (15)
Taxane-based CT	9	7 (78)	6 (67)	4 (44)
Other CT	33	21 (64)	17 (52)	6 (18)
Hormonal therapy	13	9 (69)	5 (39)	2 (15)
TKI treatment	13	7 (54)	7 (54)	1 (8)
Other targeted treatment	23	11 (48)	8 (35)	2 (9)
Concomitant radiotherapy	9	4 (44)	3 (33)	1 (11)

CT = chemotherapy, TKI = tyrosine kinase inhibitors.

Characteristics of metallic taste

Table 3 displays the responses of 19 patients (one patient reporting metallic taste did not fill out the last part of the questionnaire) to the statements concerning the characteristics of metallic taste. A high diversity was found across patients regarding the perceived intensity, the consequences regarding the ability to eat in general or certain foods, the evoked sensation, and the duration. Eight of 19 patients reported that metallic taste was one of the most negative aspects of their taste changes.

Table 3 Responses to the statements (frequency, N) concerning the characteristics of metallic taste: perceived intensity, sensation evoked by food products, continuous sensation, consequences regarding the ability to eat in general, consequences regarding the ability to eat certain foods, and duration (N = 19).

Statement	Not at all	A little	Quite a bit	Very much	I do not know
The metallic taste:					
is intense	1	13	5	-	-
becomes stronger when I eat ^a	10	4	3	1	-
is present throughout the day	4	14	1	-	-
bothers me with food in general	7	5	5	1	1
bothers me only with certain foods	6	6	4	1	2
Duration metallic taste					
	< 1 week	1 week- 1 month	1-3 months	> 3 months	I do not know
	1	7	4	4	3

^aN = 18.

Predictors of metallic taste

Logistic regression with age, gender, treatment group, and time since most recent treatment as independent variables (N = 58) showed that gender was significantly associated with metallic taste (Table 4). Women reported metallic taste more often than men. The second model (N = 37) showed that patients experiencing a metallic taste reported that they were bothered by sour and fatty foods and that everything tasted bitter, more often (Table 5). In the third model (N = 54), only the aversion to sour foods and the bitter taste remained significant related to metallic taste (Table 6).

Table 4 Predictors of metallic taste including age, gender, treatment group, and time since most recent treatment in the logistic model (N = 58).

Included	B (SE)	95% CI for Odds Ratio		
		Lower	Odds Ratio	Upper
Constant	-1.53 (0.49)			
Gender	1.53 (0.61)	1.38	4.60	15.32

Table 5 Predictors of metallic taste including age, gender, treatment group, time since most recent treatment, and factors associated with taste changes in the logistic model (N = 38).

Included	B (SE)	95% CI for Odds Ratio		
		Lower	Odds Ratio	Upper
Constant	-19.89 (8.43)			
Gender	4.88 (2.43)	1.13	130.95	15235.98
Sour food bothers me	2.78 (1.37)	1.11	16.17	234.70
Fatty food bothers me	1.99 (1.09)	0.86	7.32	62.30
Everything tastes bitter	5.28 (2.39)	1.81	195.80	21141.98

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Table 6 Predictors of metallic taste including age, gender, treatment group, time since most recent treatment, and the three questions related to metallic taste derived from the second model in the logistic model (N = 54).

Included	B (SE)	95% CI for Odds Ratio		
		Lower	Odds Ratio	Upper
Constant	-5.49 (1.59)			
Gender	2.03 (0.80)	1.59	7.59	36.36
Sour food bothers me	0.88 (0.41)	1.07	2.41	5.42
Everything tastes bitter	1.81 (0.87)	1.13	6.14	33.44

Discussion

One-third of all patients with taste changes and 16% of all patients reported metallic taste in this heterogeneous group of cancer patients. Previous studies have shown a prevalence of metallic taste in cancer patients treated with chemotherapy ranging from 10% to 78% [16-22]. Also, metallic taste in patients treated with radiotherapy has been reported previously [23]. To our knowledge, this is the first study that reports metallic taste in patients receiving targeted therapy.

Metallic taste is a much-discussed topic on cancer patient forums. Some patients who experience metallic taste ask desperately for help on these forums to obtain information regarding suitable management strategies. In the present study, the experience of metallic taste was highly variable across the patients. Metallic taste seems not to be bothersome for all patients.

Cancer patients who experienced metallic taste reported more often that everything tasted bitter. In other studies, “metallic or bitter taste” has been reported as a taste alteration instead of “metallic taste” only. Our data confirm that metallic taste and bitter taste are closely related.

Women reported metallic taste more often than men. Also, previous studies performed in cancer patients found that taste changes were more prevalent in women compared to men [7,11,16], whereas other studies found no gender differences [3,22]. A study in 89 lung cancer patients showed that women reported more often stronger sensations, while men reported weaker sensations more frequently [24]. Reasons for gender differences regarding taste changes are currently unknown. In general, there is evidence that women have a greater taste and smell sensitivity than men [25,26].

Therefore, female cancer patients may be more prone to changes in taste function than men.

The participation rate of fifty percent was quite low in the present study. Patients were asked to participate during regular outpatient visits or hospitalization. Since no extra time was scheduled for the present study, the recruitment of patients was added to the regular work of the treating physicians and nurses. Moreover, not all outpatient visits were suitable to recruit patients (e.g., after discussing progressive disease).

Patients reporting metallic taste reported that they were bothered by sour and fatty foods, more frequently. However, the association between metallic taste and the aversion to fatty foods needs to be interpreted carefully, since the sample size was small in the logistic model including factors associated with taste changes. Health care professionals can draw attention to the risk of an aversion to these foods to support patients experiencing a metallic taste. The following management strategies can be advised when patients suffer from a metallic taste: the use of plastic utensils; to eat cold or frozen foods; adding strong herbs, spices, sweetener, or acid to foods; eating sweet and sour foods; to use “miracle fruit” supplements; and to rinse with chelating agents [10]. The use of sour foods and adding sour taste to foods is in contradiction to the present finding that patients who experienced metallic taste more often reported that they were bothered by sour foods. Future studies are needed to clarify this possible relationship.

Metallic sensations have also been reported as a side effect of drugs [27] and throughout pregnancy [28]. Moreover, metallic taste might be elicited by oral yeast infections [29], burning mouth syndrome [30], damage by stapedectomy or anesthesia of the chorda tympani [31,32], artificial sweeteners [33], and dental amalgam fillings [34]. These factors may have influenced the prevalence of metallic taste in the current study. However, only patients who experienced taste changes in the preceding week completed the questionnaire with regard to metallic taste and were asked to reflect on new symptoms previously unknown to them. Therefore, the reported metallic taste may be due to drug effects or infection, but not due to the other above-mentioned causes.

In conclusion, metallic taste is a side effect of systemic therapy that is not commonly addressed by health care professionals. However, one-third of all patients with taste changes and 16% of all patients reported metallic taste during their treatment. Patients treated with chemotherapy, concomitant radiotherapy, hormonal therapy, and

other targeted therapy are all at risk of experiencing a metallic taste. However, not all patients find this type of taste alteration bothersome.

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Conflict of interest

The authors declare that they have no conflict of interest.

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Supplementary material

Questionnaire

Gender: **Male** / **Female**

Age: ____ years

1. Diagnosis (type of cancer):

If you are not receiving any treatment at the moment, please continue with question 4.

2. What type of cancer treatment are you receiving at the moment?

Please indicate the name of the medication.

In case of a combination of treatments, please specify all treatments.

3. How many courses have you received so far (in case of chemotherapy) or how long have you been on treatment (in case of other therapy)?

4. When did you receive your most recent treatment?

- a) Less than a week ago
- b) Between a week and a month ago
- c) Between a month and three months ago
- d) More than three months ago

5. Have you been treated with chemotherapy in the past?

- a) No
- b) Yes, namely:

Type(s) of chemotherapy:

Number of courses:

Period of time:

6. Are you receiving radiotherapy at the moment?

- a) No
- b) Yes

The following questions concern taste changes that you may have experienced during the course of your disease.

7. Have you experienced a change in taste since your diagnosis?

- a) No (*if this is the case, you have now completed the questionnaire*)
- b) Yes

8. What do you believe is the cause of these taste changes?

- a) The taste changes are caused by the disease
- b) The taste changes are caused by the treatment
- c) The taste changes are caused by the disease, as well as the treatment
- d) The taste changes are caused by something else
- e) I am not able to answer that

The remaining questions concern the experience of your taste during this week. If you consider your taste to be normal this week (like before the diagnosis), you do not need to fill out the rest of the questionnaire.

Could you specify to which extent each statement is applicable to you?

Please circle the number that most closely fits your condition.

	Not at all	A little	Quite a bit	Very much	I do not know
9. I feel nauseous	1	2	3	4	5
10. The smell of food bothers me	1	2	3	4	5
11. I have difficulty keeping food down	1	2	3	4	5
12. My appetite is reduced	1	2	3	4	5
13. I have a dry mouth	1	2	3	4	5
14. I have difficulty with swallowing certain foods.	1	2	3	4	5
15. Sweet food bothers me	1	2	3	4	5
16. Salty food bothers me	1	2	3	4	5
17. Sour food bothers me	1	2	3	4	5

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	Not at all	A little	Quite a bit	Very much	I do not know
18. Bitter food bothers me	1	2	3	4	5
19. My appetite is increased	1	2	3	4	5
20. I like to eat sweets	1	2	3	4	5
21. Chocolate bothers me	1	2	3	4	5
22. I have difficulty eating red meat (beef, horse, pork or lamb)	1	2	3	4	5
23. Fatty food bothers me	1	2	3	4	5
24. Hot food bothers me	1	2	3	4	5

You can proceed to the next page.

Could you indicate per taste how you perceive this taste compared to before the start of your treatment?

Please circle the number that most closely fits your condition.

	I do not taste it anymore	I have a lot of trouble tasting it	I have some trouble tasting it	It tastes normal	It tastes stronger	I do not know
25. Food in general	1	2	3	4	5	6
26. Sweet taste	1	2	3	4	5	6
27. Salty taste	1	2	3	4	5	6
28. Sour taste	1	2	3	4	5	6
29. Bitter taste	1	2	3	4	5	6

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Could you specify to which extent each statement is applicable to you?

Please circle the number that most closely fits your condition.

	Not at all	A little	Quite a bit	Very much	I do not know
30. I am unable to perceive the smell of food	1	2	3	4	5
31. Everything tastes bad	1	2	3	4	5
32. Food does not taste as it should	1	2	3	4	5
33. I have a bitter taste in my mouth	1	2	3	4	5
34. I have a bad taste in my mouth	1	2	3	4	5
35. Everything tastes bitter	1	2	3	4	5
36. I would rather eat cold food than hot food	1	2	3	4	5
37. Everything tastes good	1	2	3	4	5
38. The taste changes have a negative effect on my quality of life	1	2	3	4	5

39. Patients may experience a different taste regarding certain foods.

In such a case, the taste of certain food is different than it used to be.

Have you experienced certain foods to taste differently than before your diagnosis?

- a) I have not experienced a different taste to certain foods
- b) I have experienced a different taste to certain foods,
this taste resembles the taste of (multiple answers possible):

- ☐ Blood
- ☐ Bitter
- ☐ Something chemical
- ☐ Something musty
- ☐ Drugs
- ☐ Metallic
- ☐ Sweet
- ☐ Salty
- ☐ Sour
- ☐ Other, namely:

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40. Patients may experience a continuous taste in their mouth.

Have you experienced a continuous taste in your mouth that you did not experience before your diagnosis?

- a) I have not experienced a continuous taste in my mouth
- b) I have experienced a continuous taste in my mouth,
this taste resembles the taste of (multiple answers possible):

- ☐ Blood
- ☐ Bitter
- ☐ Something chemical
- ☐ Something musty
- ☐ Drugs
- ☐ Metallic
- ☐ Sweet
- ☐ Salty
- ☐ Sour
- ☐ Other, namely:

Please answer the following questions only if you ever experienced a metallic taste. If you never experienced a metallic taste, you have completed the questionnaire.

Could you specify for each statement to which extent it is applicable to you?

Please circle the answer that is most applicable to you.

	Not at all	A little	Quite a bit	Very much	I do not know
41. The metallic taste is intense	1	2	3	4	5
42. The metallic taste bothers me with food in general	1	2	3	4	5
43. The metallic taste bothers me only with certain foods	1	2	3	4	5
44. The metallic taste becomes stronger when I eat	1	2	3	4	5
45. The metallic taste is present throughout the day	1	2	3	4	5

46. Have you experienced this metallic taste as one of the most negative aspects of your taste changes?

- a) No
- b) Yes
- c) I do not know

47. How long have you been experiencing this metallic taste?

- a) Less than a week
- b) Between a week and a month
- c) Between a month and three months
- d) More than three months
- e) I am not able to answer that

You have completed the questionnaire. Thank you for your cooperation.

